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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/70, A61L 15/16

A1

(11) International Publication Number: WO 97/15296

(43) International Publication Date: 1 May 1997 (01.05.97)

(21) International Application Number: PCT/US96/16890

(22) International Filing Date: 22 October 1996 (22.10.96)

(30) Priority Data:
08/553,807 23 October 1995 (23.10.95) US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: BUCCAL DELIVERY OF GLUCAGON-LIKE INSULINOTROPIC PEPTIDES

(57) Abstract

Drug delivery systems and methods for administering a glucagon-like insulinotropic peptide to the buccal mucosa for transmucosal drug delivery are described. The drug delivery systems comprise a drug composition containing an effective amount of the glucagon-like insulinotropic peptide and an effective amount of a permeation enhancer for enhancing permeation of glucagon-like insulinotropic peptide through the buccal mucosa and means for maintaining the drug composition in a drug transferring relationship with buccal mucosa. These systems can be in free form, such as creams, gels, and ointments, or can comprise a device of determined physical form, such as tablets, patches, and troches. A preferred glucagon-like insulinotropic peptide is GLP-1(7-36)amide.

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BUCCAL DELIVERY OF GLUCAGON-LIKE INSULINOTROPIC PEPTIDES

Background of the Invention

This invention relates to compositions and methods for delivery of drugs, especially peptide drugs, to a warm-blooded animal by transmucosal administration and particularly through the buccal mucosa of the oral cavity. More particularly, the invention relates to compositions and methods for buccal delivery of glucagon-like insulinotropic peptides (GLIPs) into the body.

Traditionally there has been very little work evaluating membranes of the oral cavity as sites of drug administration. Both the buccal and sublingual membranes offer advantages over other routes of administration. For example, drugs administered through the buccal and sublingual routes have a rapid onset of action, reach high levels in the blood, avoid the first-pass effect of hepatic metabolism, and avoid exposure of the drug to fluids of the gastrointestinal tract. Additional advantages include easy access to the membrane sites so that the drug can be applied, localized, and removed easily. Further, there is good potential for prolonged delivery through the buccal membrane. M. Rathbone & J. Hadgraft, 74 <u>Int'l J. of Pharmaceutics</u> 9 (1991). Administration through the buccal mucosa may be better accepted than rectal dosing, for example, and generally avoids local toxic effects, such as has been a problem in nasal administration. B. Aungst & N. Rogers, 53 <u>Int'l J. Pharmaceutics</u> 227, 228 (1989).

The sublingual route has received far more attention than has the buccal route. The sublingual mucosa includes the membrane of the ventral surface of the tongue and the floor of the mouth, whereas the buccal mucosa constitutes the lining of the cheek and lips. The sublingual mucosa is relatively permeable, thus giving rapid absorption and acceptable

bioavailabilities of many drugs. Further, the sublingual mucosa is convenient, easily accessible, and generally well accepted. This route has been investigated clinically for the delivery of a substantial number of drugs. It is the traditional route for administration of nitroglycerin and is also used for buprenorphine and nifedipine. D. Harris & J. Robinson, 81 J. Pharmaceutical Sci. 1 (1992). The sublingual mucosa is not well suited to sustained-delivery systems, however, because it lacks an expanse of smooth and relatively immobile mucosa suitable for attachment of a retentive delivery system.

The buccal mucosa is less permeable than the sublingual mucosa, and the rapid absorption and high bioavailabilities seen with sublingual administration of drugs is not generally provided to the same extent by the buccal mucosa. D. Harris & J. Robinson, 81 J. Pharmaceutical Sci. 1, 2 (1992). The permeability of the oral mucosae is probably related to the physical characteristics of the tissues. The sublingual mucosa is thinner than the buccal mucosa, thus permeability is greater for the sublingual tissue. The palatal mucosa is intermediate in thickness, but is keratinized and thus less permeable, whereas the sublingual and buccal tissues are not keratinized. The buccal mucosa, however, appears well suited to attachment of retentive delivery systems.

The ability of molecules to permeate through the oral mucosae also appears to be related to molecular size, lipid solubility, and ionization. Small molecules, less than about 300 daltons, appear to cross the mucosae rapidly. As molecular size increases, however, permeability decreases rapidly. Lipid-soluble compounds are more permeable through the mucosae than are non-lipid-soluble molecules. In this regard, the relative permeabilities of molecules seems to be related to their partition coefficients. The degree of

ionization of molecules, which is dependent on the pK_a of the molecule and the pH at the membrane surface, also greatly affects permeability of the molecules. Maximum absorption occurs when molecules are unionized or neutral in electrical charge; absorption decreases as the degree of ionization increases. Therefore, charged macromolecular drugs present the biggest challenge to absorption through the oral mucosae.

Substances that facilitate the transport of solutes across biological membranes, penetration enhancers, are well known in the art for administering drugs. V. Lee et al., 8 Critical Reviews in Therapeutic Drug Carrier Systems 91 (1991) [hereinafter "Critical Reviews"]. Penetration enhancers can be categorized as (a) chelators (e.g., EDTA, citric acid, salicylates), (b) surfactants (e.g., sodium dodecyl sulfate (SDS)), (c) non-surfactants (e.g., unsaturated cyclic ureas), (d) bile salts (e.g., sodium deoxycholate, sodium taurocholate), and (e) fatty acids (e.g., oleic acid, acylcarnitines, mono- and diglycerides). The efficacy of enhancers in transporting both peptide and nonpeptide drugs across membranes seems to be positively correlated with the enhancer's hydrophobicity. Critical Reviews at 112. For example, the efficacy of bile salts in enhancing the absorption of insulin through nasal membranes is positively correlated with the hydrophobicity of the bile salts' steroid structure. Critical Reviews at 115. Thus, the order of effectiveness is deoxycholate < chenodeoxycholate < cholate < ursodeoxycholate. Conjugation of deoxycholate and cholate, but not fusidic acid derivatives, with glycine and taurine does not affect their enhancement potency. Transmucosal intestinal delivery of heparin is not apparent, as measured in terms of prolongation of partial thromboplastin time or release of plasma lipase activity, when administered through the colon of a baboon. However, significant activity is detected when

the bile salts, sodium cholate or deoxycholate, are included in the formulation. Critical Reviews at 108.

Various mechanisms of action of penetration enhancers have been proposed. These mechanisms of action, at least for peptide and protein drugs, include (1) reducing the viscosity and/or elasticity of mucus layer, (2) facilitating transcellular transport by increasing the fluidity of the lipid bilayer of membranes, (3) facilitating paracellular transport by altering tight junctions across the epithelial cell layer, (4) overcoming enzymatic barriers, and (5) increasing the thermodynamic activity of the drugs. Critical Reviews at 117-125.

Many penetration enhancers have been tested and found effective in facilitating mucosal drug administration, but hardly any penetration enhanced products have reached the market place. Reasons for this include lack of a satisfactory safety profile respecting irritation, lowering of the barrier function, and impairment of the mucociliary clearance protective mechanism. Critical Reviews at 169-70. Further, for an enhancer to function adequately, the enhancer and drug combination is preferably held in position against mucosal tissues for a period of time sufficient to allow enhancer-assisted penetration of the drug across the mucosal membrane. In transdermal and transmucosal technology, this is often accomplished by means of a patch or other device that adheres to the skin layer by means of an adhesive.

Oral adhesives are well known in the art. See, for example, Tsuk et al., U.S. Patent 3,972,995; Lowey, U.S. Patent 4,259,314; Lowey, U.S. Patent 4,680,323; Yukimatsu et al., U.S. Patent 4,740,365; Kwiatek et al., U.S. Patent 4,573,996; Suzuki et al., U.S. Patent 4,292,299; Suzuki et al., U.S. Patent 4,715,369; Mizobuchi et al., U.S. Patent 4,876,092; Fankhauser et al., U.S. Patent 4,855,142; Nagai et al., U.S. Patent

4,250,163; Nagai et al., U.S. Patent 4,226,848; Browning, U.S. Pat. No. 4,948,580; Schiraldi et al.,U.S. Reissue Patent Re.33,093; and J. Robinson, 18 Proc. Intern. Symp. Control. Rel. Bioact. Mater. 75 (1991). Typically, these adhesives consist of a matrix of a hydrophilic, e.g., water soluble or swellable, polymer or mixture of polymers that can adhere to a wet mucous surface. These adhesives may be formulated as ointments, thin films, tablets, troches, and other forms. Often, these adhesives have had medicaments mixed therewith to effectuate slow release or local delivery of a drug. Some, however, have been formulated to permit adsorption through the mucosa into the circulatory system of the individual.

Glucagon-like insulinotropic peptides, *e.g.* GLP-1(7-36)amide, are antidiabetogenic agents being investigated for treatment of diabetes mellitus that have heretofore been administered intravenously, subcutaneously, or by some other invasive route, and are too large for transdermal delivery. Diabetes mellitus afflicts nearly 15 million people in the United States. About 15 percent have insulin-dependent diabetes (IDDM; type 1 diabetes), which is believed to be caused by autoimmune destruction of pancreatic islet beta cells. In such patients, insulin therapy is essential for life. About 80% of patients have non-insulin-dependent diabetes (NIDDM; type 2 diabetes), a heterogeneous disorder characterized by both impaired insulin secretion and insulin resistance. A few patients who appear to have NIDDM may actually have a slowly progressive form of IDDM and eventually become dependent on insulin. Most patients with NIDDM, however, can be treated without insulin. They are usually overweight and have the insulin resistance of obesity superimposed on the insulin resistance intrinsic to the disease. Weight loss, especially early in the disease, can restore normal glucose levels in the blood of these

patients. Their diabetes may develop when the impact of the combined insulin resistances exceeds the ability of their pancreatic beta cells to compensate. Plasma insulin levels in such patients, which are often higher than those in people of normal weight who do not have diabetes, are not appropriate to their obesity and hyperglycemia. People with NIDDM who are not obese may have a primary defect in insulin secretion in which elevations of plasma glucose levels cause not only insulin resistance but also the further deterioration of pancreatic beta cell functioning. J.E. Gerich, Oral Hypoglycemic Agents, 321 N. Engl. J. Med. 1231 (1989).

NIDDM patients are generally treated with diet modifications and sulfonylureas and/or diguanides. H.E. Lebovitz & M.N. Feinglos, Sulfonylurea Drugs: Mechanism of Antidiabetic Action and Therapeutic Usefulness, 1 Diabetes Care 189 (1978). Oral hypoglycemic agents account for about 1 percent of all prescriptions in the United States. J.E. Gerich, 321 N. Engl. J. Med. 1231 (1989). Unfortunately, about 11-36% of NIDDM patients fail to respond well to diet and sulfonylurea therapy after one year of treatment. Within 5-7 years, about half of NIDDM patients receiving sulfonylurea treatment need to start insulin therapy. These patients tend to be resistant to insulin, thus high doses of insulin are administered, which in turn leads to hyperinsulinemia which can play a role in the development of atherosclerosis. D.A. Robertson et al., Macrovascular Disease and Hyperinsulinaemia, in Bailliere's Clinical Endocrinology and Metabolism 407-24 (M. Nattras & P.J. Hale eds., 1988).

In warm-blooded animals and humans, GLIPs stimulate insulin release, lower glucagon secretion, inhibit gastric emptying, and enhance glucose utilization. M.K. Gutniak et al., Antidiabetogenic Effect of Glucagon-Like Peptide-1 (7-36)amide in Normal Subjects and Patients with Diabetes Mellitus, 326 N. Engl. J. Med. 1316

(1992); D.M. Nathan et al., Insulinotropic Action of Glucagonlike Peptide-1-(7(37) in Diabetic and Nondiabetic Subjects, 15 Diabetes Care 270 (1992); M.A. Nauck et al., Normalization of Fasting Hyperglycaemia by Exogenous Glucagon-Like Peptide 1 (7-36amide) in Type 2 (Non-Insulin-Dependent) Diabetic Patients, 36 Diabetologia 741 (1993). Further, these peptide drugs are inherently safe since the insulinotropic effects are strictly glucose dependent, thus limiting the risk of hypoglycemia in response to therapeutic use thereof. M.A. Nauck et al., Normalization of Fasting Hyperglycaemia by Exogenous Glucagon-like Peptide 1 (7-36 amide) in Type 2 (Non-Insulin-Dependent) Diabetic Patients, 36 Diabetologia 741 (1993). These properties make such peptides serious candidates for a therapeutic drug in treatment of non-insulin dependent diabetes mellitus (NIDDM).

GLP-1(7-36)amide is a gastrointestinal hormone processed from the preproglucagon gene. Preproglucagon is a polyprotein hormone precursor comprising a 20-amino acid signal peptide and a 160-amino acid prohormone, proglucagon (PG). PG has been shown to be processed differently in the pancreas and the small intestine of man. C. Ørskov et al., Pancreatic and Intestinal Processing of Proglucagon in Man, 30 Diabetologia 874 (1987). In the pancreas, the main products are (a) glucagon (PG amino acids 33-61), (b) a glycentin-related pancreatic peptide (GRPP) (PG amino acids 1-30), and (c) a large peptide-designated major proglucagon fragment (MPGF) (PG amino acids 72-158) that contains two glucagon-like sequences. The only proglucagon derived pancreatic peptide with known biological activity is glucagon. In the small intestine, the main products of proglucagon are (a) enteroglucagon (PG amino acids 1-69), which includes the glucagon sequence of amino acids, (b) GLP-1 (PG amino acids 78-107), and (c) GLP-2 (PG amino acids 126-158). C. Ørskov et al., Proglucagon

Products in Plasma of Noninsulin-dependent Diabetics and Nondiabetic Controls in the Fasting State and after Oral Glucose and Intravenous Arginine, 87 J. Clin. Invest. 415 (1991).

A variant of GLP-1(7-36)amide, termed GLP-1(7-37), has been shown to have indistinguishable biological effects and metabolic rates in healthy individuals, D. Gefel et al., Glucagon-Like Peptide-I Analogs: Effects on Insulin Secretion and Adenosine 3',5'-Monophosphate Formation, 126 Endocrinology 2164 (1990); C. Ørskov et al., Biological Effects and Metabolic Rates of Glucagonlike Peptide-1 7-36 Amide and Glucagonlike Peptide-1 7-37 in Healthy Subjects Are Indistinguishable, 42 Diabetes 658 (1993), but GLP-1(7-36)amide is the naturally occurring form in humans, C. Ørskov et al., Complete Sequences of Glucagon-like Peptide-1 from Human and Pig Small Intestine, 264 J. Biol. Chem. 12826 (1989). It has long been believed that an endocrine transmitter produced in the gastrointestinal tract, or incretin, stimulates insulin secretion in response to food intake. Since GLP-1(7-36)amide is released during a meal and after oral glucose administration and potentiates glucose-induced insulin release, this peptide may be an important incretin. J.M. Conlon, Proglucagon-derived Peptides: Nomenclature, Biosynthetic Relationships and Physiological Roles, 31 Diabetologia 563 (1988); J.J. Holst et al., Truncated Glucagon-like Peptide 1, an Insulin-releasing Hormone from the Distal Gut, 211 FEBS Lett. 169 (1987); M. Gutniak et al., Antidiabetogenic Effect of Glucagon-like Peptide-1 (7-36)amide in Normal Subjects and Patients with Diabetes Mellitus, 326 N. Engl. J. Med. 1316 (1992).

An improved treatment regime for NIDDM patients exhibiting a secondary failure to sulfonylurea should give a satisfactory metabolic control without creating marked hyperinsulinemia. Until now, there have been no other serious candidates for a drug that can be used as

such a treatment. Glucagon-like insulinotropic peptides, such as GLP-1(7-36)amide, appear to be the most promising treatment of diabetes. J. Eng, U.S. Patent No. 5,424,286; S.E. Bjorn et al., WO 9517510; J.A. Galloway et al., EP 658568; H. Agerbk et al., WO 9505848; D.E. Danley et al., EP 619322; G.C. Andrews, WO 9325579; O. Kirk et al., WO 9318785; D.I. Buckley et al., WO 9111457; J.F. Habener, U.S. 5,118,666; J.F. Habener, WO9011296; J.F. Habener, WO 8706941; J.F. Habener, U.S. Patent No. 5,120,712. It has been found previously that the combination therapy of a GLIP and a sulfonyl urea exerts a synergistic effect on glycemia and insulin release. S. Efendic et al., WO 9318786.

R.W. Baker et al., U.S. Patent No. 5,362,496, disclose oral dosage forms for transmucosal administration of nicotine for smoking cessation therapy. Such dosage forms include a lozenge, capsule, gum, tablet, ointment, gel, membrane, and powder, which are typically held in contact with the mucosal membrane and disintegrate or dissolve rapidly to allow immediate absorption. J. Kost et al., U.S. Patent No. 4,948,587, disclose enhancement of transbuccal drug delivery using ultrasound. F. Theeuwes et al., U.S. Patent No. 5,298,017, describes electrotransport of drugs, including peptides, through buccal membrane. J.L. Haslam et al., U.S. Patent No. 4,478,822, teaches a drug delivery system that can be used for buccal delivery wherein the drug is combined with a polymer that is liquid at room temperature and semisolid or a gel at body temperature. T. Higuchi et al., U.S. Patent No. 4,144,317, discloses a shaped body for drug delivery wherein the drug is contained in an ethylene-vinyl acetate copolymer. A. Zaffaroni, U.S. Patent No. 3,948,254, describes buccal drug delivery with a device having a microporous wall surrounding a closed reservoir containing a drug and a solid drug carrier. The pores

contain a medium that controls the release rate of the drug.

In view of the foregoing, it will be appreciated that compositions and methods for prolonged buccal delivery of glucagon-like insulinotropic peptides, such as GLP-1(7-36)amide, would be significant advancements in the art.

Objects and Summary of the Invention

It is an object of the present invention to provide a dosage form and method for administering a GLIP that allow easy accessibility to the site of administration.

It is also an object of the invention to provide a dosage form and method for administering a GLIP that promotes high patient acceptance and compliance.

It is another object of the invention to provide a dosage form and method for administering a GLIP that allow for localization of dosage forms over a prolonged period to maximize drug absorption.

It is still another object of the invention to provide a dosage form and method for administering a GLIP that provide acceptable tissue compatibility of the dosage form.

These and other objects are accomplished by providing a drug delivery system for transbuccal delivery of a glucagon-like insulinotropic peptide to an individual's buccal mucosa comprising:

(a) a drug composition comprising an effective amount of a glucagon-like insulinotropic peptide and an effective amount of a permeation enhancer for enhancing permeation of the glucagon-like insulinotropic peptide through the buccal mucosa; and

(b) means for maintaining the drug composition in a drug transferring relationship with the buccal mucosa, wherein the drug composition and the maintaining means are combined in a single formulation.

The drug delivery system is preferably embodied in either a device of determined physical form, such as a tablet, patch, or troche, or in free form, such as a gel, ointment, cream, or gum. In preferred devices of determined physical form, such as a tablet or patch, the means for maintaining the drug composition in drug transferring relationship with the buccal mucosa is an adhesive.

The permeation enhancer is preferably a member selected from the group consisting of cell envelope disordering compounds, solvents, steroidal detergents, bile salts, chelators, surfactants, non-surfactants, fatty acids, and mixtures thereof. A preferred organic solvent is a member selected from the group consisting of a C_2 or C_3 alcohol, and C_3 or C_4 diol, DMSO, DMA, DMF, 1-n-dodecyl-cyclazacyclo-heptan-2-one, N-methyl pyrrolidone, N-(2-hydroxyethyl) pyrrolidone, triacetin, propylene carbonate and dimethyl isosorbide and mixtures thereof. A preferred cell-envelope disordering compound is a member selected from the group consisting of isopropyl myristate, methyl laurate, oleic acid, oleyl alcohol, glycerol monoleate, glycerol dioleate, glycerol trioleate, glycerol monostearate, glycerol monolaurate, propylene glycol monolaurate, sodium dodecyl sulfate, and sorbitan esters and mixtures thereof. A preferred bile salt is a steroidal detergent selected from the group consisting of natural and synthetic salts of cholanic acid and mixtures thereof.

A preferred tablet according to the invention comprises an adhesive layer comprising a hydrophilic polymer having one surface adapted to contact a first tissue of the oral cavity and adhere thereto when wet and an opposing surface in contact with and adhering to an adjacent drug/enhancer layer comprising the permeation enhancer and the glucagon-like insulinotropic peptide, the drug/enhancer layer adapted to contact and be in drug transfer relationship with the buccal mucosa

when the adhesive layer contacts and adheres to the first tissue, preferably the gingiva. Preferably the hydrophilic polymer comprises at least one member selected from the group consisting of hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethylcellulose, ethylcellulose, carboxymethyl cellulose, dextran, gaur-gum, polyvinyl pyrrolidone, pectins, starches, gelatin, casein, acrylic acid polymers, polymers of acrylic acid esters, acrylic acid copolymers, vinyl polymers, vinyl copolymers, polymers of vinyl alcohols, alkoxy polymers, polyethylene oxide polymers, polyethers, and mixtures thereof. It is also preferred that the adhesive layer additionally contain one or more members selected from the group consisting of fillers, tableting excipients, lubricants, flavors, and dyes and that the drug/enhancer layer additionally contain one or members selected from the group consisting of tableting excipients, fillers, flavors, taste-masking agents, dyes, stabilizers, enzymer inhibitors, and lubricants. A preferred glucagon-like insulinotropic peptide is GLP-1(7-36)amide. Such a tablet is disclosed and claimed in U.S. Patent Application Serial No. (filed of even date herewith).

Another form of bilayer tablet which may suitably be used is disclosed in U.S. Patent 5,346,701.

Another preferred device of determined physical form is a transbuccal patch, which can be either a matrix patch or a reservoir patch. In a preferred matrix patch, the glucagon-like insulinotropic peptide and permeation enhancer are suspended or dispersed in the adhesive. In a preferred reservoir patch, the glucagon-like insulinotropic peptide and permeation enhancer are contained in the reservoir. Typical of such matrix and reservoir patches are those illustrated in U.S. Patents 4,849,224; 4,983,395; 5,122,383; 5,202,125; 5,212,199; 5,227,169; 5,302,395 5,346,701.

The drug composition of the present invention can also further comprise an effective amount of a sulfonyl urea.

A method of delivering a glucagon-like insulinotropic peptide for transbuccal drug delivery to an individual's buccal mucosa comprises bringing the buccal mucosa into contact with a delivery system comprising:

(a) a drug composition comprising an effective amount of the glucagon-like insulinotropic peptide and an effective amount of a permeation enhancer for enhancing permeation of the glucagon-like insulinotropic peptide through the buccal mucosa; and

(b) means for maintaining the drug composition in a drug transferring relationship with the buccal mucosa, wherein the drug composition and the maintaining means are combined in a single formulation;

and retaining said delivery system in contact with said mucosa for a time sufficient to delivery an effective amount of said peptide to said individual.

A method of treating diabetes comprises delivering a glucagon-like insulinotropic peptide for transbuccal delivery to an individual's buccal mucosa comprising bringing the buccal mucosa into contact with a delivery system comprising:

(a) a drug composition comprising an effective amount of the glucagon-like insulinotropic peptide and an effective amount of a permeation enhancer for enhancing permeation of the glucagon-like insulinotropic peptide through the buccal mucosa; and

(b) means for maintaining the drug composition in a drug transferring relationship with the buccal mucosa, wherein the drug composition and the maintaining means are combined in a single formulation;

and retaining said delivery system in contact with said mucosa for a time sufficient to delivery an effective amount of said peptide to said individual.

Brief Description of the Drawings

FIG. 1 shows a schematic sectional view of a bilayer tablet dosage form according to the present invention wherein a drug-containing layer thereof is in drug-transfer relationship with buccal mucosa.

FIG. 2 shows a schematic sectional view of a matrix patch embodiment having an optional adhesive overlay according to the present invention.

FIG. 3 shows a schematic sectional view of a liquid reservoir patch according to the present invention.

FIG. 4 shows the results of blood glucose determinations for fasting subjects given a placebo (dotted line) or GLP-1(7-36)amide (solid line) by buccal administration of a bilayer tablet according to the present invention.

FIG. 5 shows the results of plasma insulin determinations for subjects given a placebo (○) or GLP-1(7-36)amide (●) by buccal administration of a bilayer tablet according to the present invention.

FIG. 6 shows the results of plasma glucagon determinations for subjects given a placebo (○) or GLP-1(7-36)amide (●) by buccal administration of a bilayer tablet according to the present invention.

FIG. 7 shows the results of plasma GLP-1(7-36)amide determinations for subjects given a placebo (dotted line) or the drug (solid line) by buccal administration of a bilayer tablet according to the present invention.

FIG. 8 shows the results of plasma GLP-1 determinations for fasting subjects given the drug by subcutaneous administration at various doses: (◆) placebo; (■) 0.15 nmol/kg; (▲) 0.50 nmol/kg; (X) 1.50 nmol/kg; (*) 4.50 nmol/kg.

Detailed Description of the Invention

Before the present compositions and methods for buccal delivery of a glucagon-like insulinotropic peptide are disclosed and described, it is to be

understood that this invention is not limited to the particular formulations, process steps, and materials disclosed herein as such formulations, process steps, and materials may vary somewhat. It is also to be understood that the terminology employed herein is used for the purpose of describing particular embodiments only and is not intended to be limiting since the scope of the present invention will be limited only by the appended claims and equivalents thereof.

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to a bilayer tablet containing "a glucagon-like insulinotropic peptide" includes a mixture of two or more of such peptides, reference to "an adhesive" includes reference to one or more of such adhesives, and reference to "a bile salt" includes reference to a mixture of two or more of such bile salts.

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

As used herein, "glucagon-like insulinotropic peptide" or "GLIP" means insulinotropic peptides that exhibit substantial amino acid sequence similarity to glucagon, such as GLP-1(7-36)amide and precursors, analogues, and fragments thereof wherein said precursors, analogues, and fragments have insulinotropic, or insulin stimulating, activity. Such precursors, analogues, and fragments include polypeptides having the primary sequence of GLP-1(7-36)amide wherein one or more L-amino acid residues are coupled to the C-terminus or N-terminus thereof, *e.g.* GLP-1(7-37); wherein the C-terminus contains a carboxyl group, an amide or substituted amide, an ester, or salt; and combinations thereof. Also included in the

definition are peptides substantially homologous to GLP-1(7-36)amide and analogues thereof, provided such homologous peptides also contain insulinotropic activity. As used herein, "substantially homologous" refers to peptides that retain functionality despite differences in primary structure from peptides to which they are compared. For example, a peptide substantially homologous to GLP-1(7-36)amide is one that retains functionality as an insulinotropic agent although it may include additional amino acid residues or be a truncation, deletion variant, or substitution variant thereof. A substitution variant is one that contains a conservative substitution of one or more amino acid residues. A conservative substitution is a substitution of one amino acid residue for another wherein functionality of the peptide is retained, in this case, functionality as an insulinotropic agent. Amino acid residues belonging to certain conservative substitution groups can sometimes substitute for another amino acid residue in the same group. One such classification of conservative substitution groups is as follows: (a) Pro; (b) Ala, Gly; (c) Ser, Thr; (d) Asn, Gln; (e) Asp, Glu; (f) His; (g) Lys, Arg; (h) Cys; (i) Ile, Leu, Met, Val; and (j) Phe, Trp, Tyr. M. Jimenez-Montano & L. Zamora-Cortina, Evolutionary model for the generation of amino acid sequences and its application to the study of mammal alpha-hemoglobin chains, Proc. VIIth Int'l Biophysics Congress, Mexico City (1981). Another such classification is described in M. Dayhoff et al., Atlas of Protein Sequence and Structure 1978 (Nat'l Biomed. Res. Found., Washington, D.C.), hereby incorporated by reference. Other variations that are to be considered substantially homologous include substitution of D-amino acids for the naturally occurring L-amino acids, substitution of amino acid derivatives such as those containing additional side chains, and substitution of non-standard amino acids, i.e. α-amino acids that are

rare or do not occur in proteins. The primary structure of a substantially homologous peptide is thus limited only by functionality.

As used herein, "peptide" means peptides of any length and includes proteins. The terms "polypeptide" and "oligopeptide" are used herein without any particular intended size limitation, unless a particular size is otherwise stated.

As used herein, "chemical enhancer," "penetration enhancer," "permeation enhancer," and the like shall be inclusive of all enhancers that increase the flux of a permeant, drug, or other molecule across the mucosa and is limited only by functionality. In other words, all cell envelope disordering compounds, solvents, steroidal detergents, bile salts, chelators, surfactants, non-surfactants, fatty acids, and any other chemical enhancement agents are intended to be included.

The flux of a drug or analyte across the mucosa can be increased by changing either the resistance (the diffusion coefficient) or the driving force (the gradient for diffusion). Flux may be enhanced by the use of so-called penetration or permeation or chemical enhancers.

Permeation enhancers are comprised of two primary categories of components, i.e., cell-envelope disordering compounds and solvents or binary systems containing both cell-envelope disordering compounds and solvents. As discussed above, other categories of permeation enhancer are known, however, such as steroidal detergents, bile salts, chelators, surfactants, non-surfactants, and fatty acids.

Cell envelope disordering compounds are known in the art as being useful in topical pharmaceutical preparations and function also in drug delivery through the skin or mucosa. These compounds are thought to assist in dermal penetration by disordering the lipid structure of the stratum corneum cell-envelopes. A list

of such compounds is described in European Patent Application 43,738, published June 13, 1982, which is incorporated herein by reference. It is believed that any cell envelope disordering compound is useful for purposes of this invention. Exemplary of the cell envelope disordering compounds are those represented by the formula:

R-X

wherein R is a straight-chain alkyl of about 7 to 16 carbon atoms, a non-terminal alkenyl of about 7 to 22 carbon atoms, or a branched-chain alkyl of from about 13 to 22 carbon atoms, and X is -OH, $-COOCH_3$, $-COOC_2H_5$, $-OCOCH_3$, $-SOCH_3$, $-P(CH_3)_2O$, $-COOC_2H_4OC_2H_4OH$, $-COOCH(CHOH)_4CH_2OH$, $-COOCH_2CHOHCH3$, $-COOCH_2CH(OR'')CH_2OR''$, $-(OCH_2CH_2)_mOH$, -COOR', or $-CONR'_2$ where R' is -H, $-CH_3$, $-C_2H_5$, $-C_3H_7$ or $-C_2H_4OH$; R" is -H, or a non-terminal alkenyl of about 7 to 22 carbon atoms; and m is 2-6; provided that when R" is an alkenyl and X is -OH or -COOH, at least one double bond is in the cis-configuration.

Suitable solvents include water; diols, such as propylene glycol and glycerol; mono-alcohols, such as ethanol, propanol, and higher alcohols; DMSO; dimethylformamide; N,N-dimethylacetamide; 2-pyrrolidone; N-(2-hydroxyethyl) pyrrolidone, N-methylpyrrolidone, 1-dodecylazacycloheptan-2-one and other n-substituted-alkyl-azacycloalkyl-2-ones (azones) and the like.

U.S. Patent 4,537,776, Cooper, issued August 27, 1985, contains an excellent summary of prior art and background information detailing the use of certain binary systems for permeant enhancement. Because of the completeness of that disclosure, the information and terminology utilized therein are incorporated herein by reference.

Similarly, European Patent Application 43,738, referred to above, teaches using selected diols as solvents along with a broad category of cell-envelope

disordering compounds for delivery of lipophilic pharmacologically-active compounds. Because of the detail in disclosing the cell-envelope disordering compounds and the diols, this disclosure of European Patent Application 43,738 is also incorporated herein by reference.

A binary system for enhancing metoclopramide penetration is disclosed in UK Patent Application GB 2,153,223 A, published August 21, 1985, and consists of a monovalent alcohol ester of a C8-32 aliphatic monocarboxylic acid (unsaturated and/or branched if C18-32) or a C6-24 aliphatic monoalcohol (unsaturated and/or branched if C14-24) and an N-cyclic compound such as 2-pyrrolidone, N-methylpyrrolidone and the like.

Combinations of enhancers consisting of diethylene glycol monoethyl or monomethyl ether with propylene glycol monolaurate and methyl laurate are disclosed in U.S. Patent 4,973,468 as enhancing the transdermal delivery of steroids such as progestogens and estrogens. A dual enhancer consisting of glycerol monolaurate and ethanol for the transdermal delivery of drugs is shown in U.S. Patent 4,820,720. U.S. Patent 5,006,342 lists numerous enhancers for transdermal drug administration consisting of fatty acid esters or fatty alcohol ethers of C_2 to C_4 alkanediols, where each fatty acid/alcohol portion of the ester/ether is of about 8 to 22 carbon atoms. U.S. Patent 4,863,970 shows penetration-enhancing compositions for topical application comprising an active permeant contained in a penetration-enhancing vehicle containing specified amounts of one or more cell-envelope disordering compounds such as oleic acid, oleyl alcohol, and glycerol esters of oleic acid; a C_2 or C_3 alkanol and an inert diluent such as water.

Other permeation enhancers, not necessarily associated with binary systems include DMSO or aqueous solutions of DMSO such as taught in Herschler, U.S.

Patent 3,551,554; Herschler, U.S. Patent 3,711,602; and Herschler, U.S. Patent 3,711,606, and the azones (n-substituted-alkyl-azacycloalkyl-2-ones) such as noted in Cooper, U.S. Patent 4,557,943.

As used herein, "bile salts" means the steroidal detergents that are the natural or synthetic salts of cholanic acid, *e.g.* the salts of cholic and deoxycholic acid or combinations of such salts, and the unionized acid form is also included. The salts of the conjugates of the bile acid with glycine or taurine are preferred, with the taurine salts being particularly preferred. Bile salt analogs having the same physical characteristics and that also function as permeation enhancers are also included in this definition. "NaTC" is the bile salt, sodium taurocholate. "CHAPS" is the bile salt analog, 3-[3-cholamidopropyl)dimethylammonio]-1-propane sulfate, inner salt.

As used herein, "transmucosal," "transbuccal," and similar terms mean passage of a glucagon-like insulinotropic peptide into and through the buccal mucosa to achieve effective therapeutic blood levels or deep tissue levels thereof.

As used herein, "effective amount" means an amount of a glucagon-like insulinotropic peptide that is nontoxic but sufficient to provide a selected systemic effect and performance at a reasonable benefit/risk ratio attending any medical treatment. An effective amount of a permeation enhancer, as used herein, means an amount selected so as to provide the selected increase in mucosal permeability and, correspondingly, the desired depth of penetration, rate of administration, and amount of drug delivered.

As used herein, "adhesive," "adhesive polymer", "mucoadhesive", or such similar terms refers to hydrophilic polymers, natural or synthetic, which, by the hydrophilic designation, can be either water soluble or swellable and which are compatible with the enhancers

and glucagon-like insulinotropic peptides. Such adhesives function for adhering the dosage forms to the mucous tissues of the oral cavity, such as the gingiva. Such adhesives are inclusive of hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxy ethylcellulose, ethylcellulose, carboxymethyl cellulose, dextran, gaur gum, polyvinyl pyrrolidone, pectins, starches, gelatin, casein, acrylic acid polymers, polymers of acrylic acid esters, acrylic acid copolymers, vinyl polymers, vinyl copolymers, polymers of vinyl alcohols, alkoxy polymers, polyethylene oxide polymers, polyethers, and mixtures thereof, and the like.

By "system", "drug delivery system", "transmucosal delivery system" or the like is meant a unit dosage form of a drug composition, including carriers, enhancers, and other components, which drug composition is contained in or accompanied by means for maintaining the drug composition in a drug transferring relationship with the buccal mucosa. Such means can be either a patch, tablet, troche, or other device of determined physical form to be held against the buccal mucosa for continuous drug administration thereto for systemic transport, or such means can be formulated in free form to be applied directly to the buccal mucosa as a cream, gel, gum, ointment and the like. The term "troche" includes pastille, lozenge, morsulus, rotula, trochiscus, and the like. "Free form" means that the formulation is spreadable or malleable into a selected shape at the time of application. "Determined physical form" means that the formulation has a form determined by a device. Preferably the means used will be a device such as a tablet or matrix or liquid reservoir patch. A matrix patch contains the drug, permeation enhancer, and other optional ingredients suspended or dispersed in an adhesive layer. A reservoir patch contains the drug, permeation enhancer, and other optional ingredients in a reservoir, which can be in liquid form, or the liquid

can be gelled or thickened by an agent such as mineral oil, petroleum jelly and various aqueous gelling agents and hydrophilic polymers. Such a reservoir or matrix patch is brought into contact with the buccal mucosa and is held in place by a suitable adhesive. In a reservoir patch, the drug composition is applied to the buccal mucosa through a permeable membrane forming the reservoir floor that is in direct contact with the buccal mucosa.

The method of application of the present invention can vary within limits, but necessarily involves applying the selected drug composition to the buccal mucosa such that drug delivery is initiated and continues for a period of time sufficient to provide the selected pharmacological or biological response.

<u>Bilayer Tablets for Delivery of GLIP</u>

Referring to FIG. 1 there is shown an illustrative dosage form according to the present invention for administering GLIP through the buccal mucosa. This dosage form is provided as a bilayer tablet 10 such that drug/adhesive interactions that inhibit efficient transmembrane flux of GLIP through the mucosal tissue are greatly diminished or eliminated. The bilayer tablet 10 comprises an adhesive layer 12 and an active or drug-containing layer 14. The adhesive layer 12 is formulated to adhere to a mucous surface in the oral cavity such that the active layer 14 is in a drug-transfer relationship with a mucosal tissue, such as the buccal mucosa, such that the drug permeates through the mucosal tissue and is absorbed into the bloodstream of the individual. In the illustrative embodiment of FIG. 1, the tablet 10 is placed in the oral cavity such that the adhesive layer 12 adheres to a gingival (keratinized) surface 16 and the active layer 14 is in drug-transfer relationship with the buccal mucosa 18.

Bilayer tablets are made by classical bilayer tablet compression techniques on a suitable press. In reference to FIG. 1, the bilayer tablets 10 consist of an adhesive layer 12 and an active or drug-containing layer 14, which can be of a different color to distinguish the layers for purposes of application. The identification of the drug-containing, non-adhesive layer 14 facilitates application by the patient and prevents incidental adhesion of other oral tissues to the tablet. The adhesive layer 12 is prepared by either dry mixing the ingredients and compressing them into a tablet or by wet granulating the ingredient mixture and then compressing according to accepted pharmaceutical techniques. In general, it has been found suitable to mix the adhesive polymer or polymers and any formulation aids such as fillers, tableting excipients, lubricants, flavors, dyes, and the like and then compress the mixture in a press.

The drug-containing or active layer 14 is first prepared by intimately admixing the drug with a permeation enhancer and any other formulation aids such as tableting excipients, dyes, flavors, taste-masking agents, stabilizers, enyzmer inhibitors, lubricants, and the like. This can be formulated as a dry mix or accomplished by conventional wet granulation and screening techniques followed by drying. In either event, the blended drug-containing layer ingredients are then placed on top of the partially compressed adhesive layer and both layers are then compressed. A person of ordinary skill in the art will recognize that the instant tablet can also be manufactured by making the drug-containing layer first and then the adhesive layer.

The compositions of the present invention will preferably be sized to provide between about 0.05 to 10 cm^2 of surface area for contact between the drug-containing layer and the mucosa. Areas of between about 0.07 to 5 cm^2 are preferred with areas of between about

0.18 and 5 cm² being optimal. The drug-containing or active layer will generally have a thickness of between about 0.1 and 3 mm with thicknesses of between about 0.5 and 2 mm being preferred.

The following examples are illustrative of methods of preparing bilayer tablets according to the present invention.

Example 1

Bilayer tablets are prepared in the following manner. An adhesive layer was prepared by weighing 70 parts by weight polyethylene oxide (Polyox 301N; Union Carbide), 20 parts by weight polyacrylic acid (Carbopol 934P; B.F. Goodrich), and 10 parts by weight of a compressible xylitol/carboxymethyl cellulose filler (Xylitab 200; Xyrofin). These ingredients were mixed by rolling in a jar for 3 minutes. The mixture was then transferred to an evaporating dish and quickly wet granulated with absolute ethanol to a semi-dough-like consistency. This mass was immediately and rapidly forced through a 14 mesh (1.4 mm opening) stainless steel screen, to which the wet granules adhered. The screen was covered with perforated aluminum foil, and the wet granules were dried overnight at 30°C. The dried granules were removed from the screen and then passed through a 20 mesh (0.85 mm opening) screen to further reduce the size of the granules. Particles that did not pass through the 20 mesh screen were ground briefly with a mortar and pestle to minimize the amount of fines and then passed through the 20 mesh screen. The resulting granules were then placed in a mixing jar, and 0.25 parts by weight stearic acid and 0.06 parts by weight mint flavor (Universal Flavors) were added and blended to the granules. The final percentages by weight of the ingredients were thus 69.78% polyethylene oxide, 9.97% compressible xylitol/carboxymethyl cellulose filler, 19.94% polyacrylic acid, 0.25% stearic

acid, and 0.06% mint flavor. A 50 mg amount of this mixture was placed on a 0.375 inch diameter die and precompressed on a Carver Press Model C with 0.25 metric ton pressure for a 3 second dwell time to form the adhesive layer.

The active layer was prepared by weighing 49.39 parts by weight of mannitol, 34.33 parts by weight of hydroxypropyl cellulose (Klucel LF; Aqualon, Wilmington, Delware) and 15.00 parts by weight of sodium taurocholate (Aldrich, Milwaukee, Wisconsin), and mixing by rolling in a jar for 3 minutes. The mixture was then transferred to an evaporating dish and quickly wet granulated with absolute ethanol to a semi-dough-like consistency. This mass was immediately and rapidly forced through a 14 mesh stainless steel screen, to which the wet granules adhered. The screen was covered with perforated aluminum foil, and the granules were dried at 30°C. The dried granulation was then passed sequentially through 20, 40 (0.425 mm opening), and 60 (0.25 mm opening) mesh screens to reduce particle size further. Particles that did not pass through a screen were briefly ground with a mortar and pestle to minimize fines and then passed through the screen. The screened particles were weighed, and then 0.91 parts by weight of GLP-1(7-36)amide and 0.06 parts by weight of FD&C yellow #6HT aluminum lake dye were sequentially blended with the dry granulation by geometric dilution. The dyed granulation was then placed in a mixing jar and blended with 0.25 parts by weight magnesium stearate (lubricant) and 0.06 parts by weight mint flavor by rolling for 3 minutes. A 50 mg sample of this material was placed on top of the partially compressed adhesive layer and both layers were then compressed at 1.0 ton pressure for a 3 second dwell time to yield a bilayer tablet suitable for buccal delivery.

This procedure results in a gingival tablet wherein the active layer contains 0.91% by weight of GLP-1(7-

36)amide, 15% by weight of NaTC, and 84.09% by weight of filler, lubricant, colorant, formulation aids, or flavoring agents.

Example 2

The procedure of Example 1 was followed with the exception that the amounts of the components of the active layer were varied to provide an active layer containing 65.30% by weight mannitol, 34.33% hydroxypropyl cellulose, 0.25% magnesium stearate, 0.06% FD&C yellow #6HT aluminum lake dye, and 0.06% mint flavor. This procedure results in placebo tablets suitable for use in double-blind *in vivo* studies with human volunteers.

Example 3

The procedure of Example 1 was followed to prepare a buccal tablet wherein the active layer contained the same content but was prepared by dry blending and not by wet granulation.

<u>Buccal Patch for Delivery of GLIP</u>

FIG. 2 shows an illustrative filmpatch embodiment for buccal delivery of GLIP wherein the patch 20 consists of an underlying drug/enhancer/polymer layer 21 and an outer inert membrane layer 22 having the same diameter as active layer 21. However, the outer inert layer of a patch may extend beyond the outer periphery of the underlying active layer and have contained on the under surface thereof, additional mucoadhesive (not shown) or, as shown in FIG. 2, there may be an optional overlay 23 containing a mucoadhesive on the inner surface of overlay 23 which extends beyond the outer periphery of both the active layer 21 and the inert membrane layer 22. In this manner, the active or inner layer is completely surrounded by the overlying membrane which adheres to the mucosa and further insures that the

drug/enhancer combination will remain in the area of the oral mucosa in which it is applied until the drug/enhancer portions of the layer have been adequately delivered. The optional overlay 23 may also be a perm-selective membrane having a desired molecular weight cutoff (MWCO) pore structure. In certain instances it may be beneficial to have both membrane 22 and overlay 23 both be MWCO membranes, each having a different MWCO value for controlling or varying the amount or degree of water or other materials passing through such membranes.

FIG. 3 shows an illustrative liquid reservoir patch that can be used according to the present invention for delivering a glucagon-like insulinotropic peptide to the buccal mucosa. This liquid reservoir patch is described in U.S. Patent No. 4,849,224, hereby incorporated by reference. As described in that patent, such devices, shown generally at 24 in FIG. 3 are comprised of an uppermost layer of a heat-sealable backing film 26 having an inverted, cup-shaped recess that serves as the reservoir 28 for the drug composition. The underside of the outer edge of the backing film carries a ring-shaped layer 30 of an adhesive peripheral to the reservoir. Underlying the reservoir, just inward of the peripheral ring of adhesive is a membrane layer 32 that is permeable to the drug composition. A peel sealable inner liner 34 underlies membrane 32 and portions of backing film 26. A peel-sealable release liner 36 covers the entire underside of the assembly and forms the basal surface of the device. Device 18 has a heat seal 38 between the membrane and backing film. An alternative liquid reservoir-type device that can be used in conjuction with the present invention is described in U.S. Patent No. 4,983,395, hereby incorporated by reference.

Example 4

A buccal patch formulation is prepared containing 400 μg of GLP-1(7-36)amide using a 500 MWCO dialysis membrane as the outer covering or layer. To a vial are added 278.3 μl of a 30% by weight NaTC aqueous solution and 59 μl of 1.2% by weight GLP-1(7-36)amide aqueous solution. The solutions are stirred together until a clear solution is formed. To this is added an ethanol solution containing 1130.8 μl of 19.85% hydroxypropyl cellulose with stirring until a homogeneous mixture is obtained. A 718 μl portion of this mixture is then cast onto a 500 MWCO dialysis membrane, which has been dried in an oven at 70°C to provide a dry substrate, in a glass mold and allowed to dry overnight. Excess membrane is trimmed from around the translucent homogeneous active layer to yield a finished buccal patch having a surface area of about 5 cm^2. The active layer of this patch contains 400 μg of GLP-1(7-36)amide (4.8% by weight), 45 mg of NaTC (15% by weight), and 100.4 mg of hydroxypropyl cellulose (34% by weight).

Example 5

Troche for Delivery of GLIP

A troche for buccal delivery of a glucagon-like insulinotropic peptide is made by incorporating 400 μg of GLP-1(7-36)amide, in a mass made of a sugar and mucilage and also containing 15% by weight of NaTC, and then air drying the mixture as is well known in the art of making troches.

Example 6

Free Form Dosage Form for Delivery of GLIP

A dosage form in free form for delivery of a glucagon-like insulinotropic peptide is made by incorporating 400 μg of GLP-1(7-36)amide in a liquid

mixture comprising about 15% by weight of NaTC, and 85% by weight of water. To 12 ml of this mixture was added 0.15 g of Carbopol 1342 acrylic acid copolymer. This mixture was homogenized to result in a gelled drug composition.

In Vivo Testing of GLIP Delivery

Example 7

This example describes a double-blind, placebo-controlled, crossover comparison with random assignment to treatment sequence. Eight healthy volunteers were selected for this *in vivo* study of blood glucose, insulin, glucagon, and GLP-1(7-36)amide levels in response to receiving either a drug-containing bilayer tablet containing 400 μg of GLP-1(7-36)amide or a placebo prepared according to Examples 1 and 2, respectively. Inclusion criteria for the volunteers were normal glucose tolerance, weight within 22<BMI<26, informed consent to participate in the study, and age between 20 and 60 years. Exclusion criteria were impaired glucose tolerance (2-hour glucose tolerance test; OGTT), gastrointestinal symptoms, ongoing medication or illness, acute infection, abnormal laboratory variables (hemoglobin, hematocrit, leucocytes, creatinine, bilirubin, calcium, potassium, sodium, alkaline phosphatase, gamma-GT, SGOT, SGPT, cholesterol, and triglycerides), and blood pressure greater than 185 mmHg systolic and/or 90 mmHg diastolic.

Subject numbers were allotted to the subjects in the order in which they were enrolled in the study. The number allotted to each subject determined the treatment sequence received. Subjects receiving treatment sequence 1 were treated with drug followed by placebo, and subjects receiving treatment sequence 2 were treated with placebo followed by drug.

Subjects were instructed to fast the night before a treatment. At the clinic, the subjects were given

either a drug-containing bilayer tablet or placebo. At time 0 the bilayer tablet was applied to the gingiva with the active layer in contact with the tissue of the lip or inside of the cheek, and the subjects were placed in a rest position. The bilayer tablet was removed after 4.5 hours. No meals were allowed until a standard meal was given after 4.5 hours, and snacks were not permitted at any time. The standard meal contained 550 kcal, with 28%, 22%, and 50% of the energy from protein, fat, and carbohydrate, respectively. The test continued until 8 hours after application of the bilayer tablet, and the subjects left the hospital after 9 hours. The subjects were given their medications in the clinic by a nurse and were under observation at all times. Any symptoms or sensations disturbing or impairing the subjects' wellbeing during the experiments was carefully documented. Standard safety variables were determined under fasting conditions before each experiment. Blood glucose was monitored frequently and glucose infusion was available in case of hypoglycemia (<2.5 mmol/L). If any subject were to experience hypoglycemic symptoms, an extra blood glucose determination would be taken for safety reasons. A washout period of 1-4 days was allowed between each experiment. The study was completed within 6 weeks after enrollment of the first volunteer.

Blood samples were taken for pharmacokinetic analysis 10 minutes before application of the drug, and at 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90, 120, 150, 180, 210, 240, and 270 minutes and 6 and 8 hours after application of the drug. Samples were frozen until assayed for GLP-1(7-36)amide content by double antibody radioimmunoassay (RIA). The peptide content of bilayer tablet samples was also analyzed by HPLC. Average blood glucose, insulin, glucagon, and GLP-1(7-36)amide concentrations were calculated by area under the curve (AUC) using the trapezoidal rule. The maximal

concentration (C_{max}), half-life ($T_{½}$), and time to maximal blood level (T_{max}) were calculated for GLP-1(7-36)amide based on plasma levels of the peptide. Results were tested for normal distribution. A two-tailed t-test was carried out for normally distributed samples, and a Wilcoxon rank-sum test was used for data that were not normally distributed. All statistical tests used a level of significance of 0.05.

FIG. 4 shows the results of blood glucose determinations for subjects given the placebo (dotted line) or drug (solid line). For the placebo group, blood glucose levels remain relatively constant from 10 minutes before application of the bilayer tablet through 270 minutes after application thereof. Over the same time period, the blood glucose levels of subjects receiving GLP-1(7-36)amide drop below that of the placebo group by 20 minutes after application of the drug, reach a lowest level of about 3 mmol/L at about 50 minutes, and return to a normal level by about 90 minutes. Blood glucose levels of the two groups are indistinguishable after the meal. These data show that buccal administration of GLP-1(7-36)amide with the bilayer tablet according to the present invention results in significantly reduced blood glucose levels as compared to placebo controls.

FIG. 5 shows the results of plasma insulin determinations for subjects given the placebo (○) or the drug (●). For the placebo group, the plasma insulin levels remain relatively constant or decline slightly over the course of 10 minutes prior to administration of the bilayer tablet to 270 minutes after administration thereof. For the group receiving GLP-1, the plasma insulin level rises sharply from a normal level at 10 minutes after administration of the drug to a level about three time normal at 15 minutes after administration. A peak plasma insulin level is reached about 20 minutes after administration of GLP-1(7-

36)amide, and the level rapidly declines to normal by about 50 minutes. Otherwise, the insulin levels of the drug group track the insulin levels of the placebo group. Thus, buccal administration of GLP-1(7-36)amide results in a rapid increase of plasma insulin concentration followed by a rapid decrease, both within an hour of administration of the drug.

FIG. 6 shows the results of plasma glucagon determinations for subjects given the placebo (O) or the drug (●). For the placebo group, the plasma glucagon level declines slowly and steadily from 10 minutes prior to administration of the bilayer tablet until 270 minutes after administration thereof. For the drug group, the plasma glucagon level declines sharply from time 0 until a level significantly lower than the placebo group is reached about 30 minutes later, and then the level rises sharply to a level significantly higher than the placebo group, reaching a peak about 60-75 minutes after administration. From this peak, the plasma glucagon level declines steadily until it tracks the level of the placebo group beginning at about 150 minutes after administration of the drug. These data show that buccal administration of GLP-1(7-36)amide quickly lowers plasma glucagon levels below those of the placebo group and then raises them to higher than normal levels before they reach normal levels again about 150 minutes after administration.

FIG. 7 shows the results of plasma GLP-1(7-36)amide determinations for subjects given the placebo (dotted line) or drug (solid line). For the placebo group, the amount of GLP-1(7-36)amide in the plasma remains fairly constant at a very low level from 10 minutes prior to administration of the drug until 270 minutes after administration thereof. After the meal, the plasma GLP-1(7-36)amide level rises and then declines steadily over time. For the drug group, the plasma GLP-1(7-36)amide level rises sharply beginning within 5 minutes of

administration and reaches a peak about 30 minutes after administration. The GLP-1(7-36)amide level then declines rapidly until about 90 minutes after administration, and then declines more slowly to a level that tracks that of the placebo group beginning at about 150 minutes. After the meal, the GLP-1(7-36)amide level is approximately the same as that of the placebo group. These results show that buccal administration of GLP-1(7-36)amide results in rapid absorption through the buccal mucosa into the bloodstream and that elevated levels of GLP-1(7-36)amide remain in the blood until about 150 minutes after administration.

Taken together, these data show that buccal administration of GLP-1(7-36)amide with the bilayer tablet of the instant invention results in rapid absorption into the bloodstream that leads to a sharp rise in the amount of plasma insulin and a corresponding decrease in the amount of glucose in the blood. Further, the blood glucose level does not result in hypoglycemia, probably because of the above-mentioned glucose dependence of the insulinotropic effects of the drug.

Example 8

In this example, the relative bioavailability of GLP-1(7-36)amide by buccal administration is compared to that of subcutaneously administered GLP-1. This was done in comparison to published data. Two studies providing intravenous infusion data in fasting individuals are available: D.M. Nathan et al., Insulinotropic Action of Glucagonlike peptide-1-(7-37) in Diabetic and Nondiabetic Subjects, 15 Diabetes Care 270 (1992); C. Ørskov et al., Biological Effects and Metabolic Rates of Glucagonlike Peptide-1 7-36 amide and Glucagonlike Peptide-1 7-37 in Healthy Subjects is Indistinguishable, 42 Diabetes 658 (1993). Both of

these studies support an approximate clearance of 15 ml/min/kg.

A study by M.A. Nauck of subcutaneous administration of GLP-1 to fasting subjects illustrates changes in the pharmocokinetics with dose (FIG. 8). This could be due to changes in bioavailability with dose, changes in clearance with dose, or a combination of both effects. At any rate, regression analysis of all the results indicate a clearance of about 40 ml/min/kg, which is consistent with a bioavailability of 38% by subcutaneous administration relative to intravenous administration.

The data summarized in FIG. 7 were analyzed by AUC to provide an estimate of relative bioavailability by buccal administration as compared to subcutaneous administration. These data are shown in Table 1.

Table 1

GLP-1(7-36)amide Pharmacokinetic Summary - Buccal Delivery

Subject	Dose (nmol)	AUC (pmol-min/L)	Dose (nmol)	Bioavail-ability (%)	Half-Life (30-210 min)
901	119	9113	9.57	8.04	27.13
902	119	7250	7.61	6.40	23.99
903	119	8753	9.19	7.72	29.49
904	119	--	--	--	--
905	119	8410	8.83	7.42	18.80
906	119	11343	11.91	10.01	24.38
907	119	3278	3.44	2.89	29.95
908	119	--	--	--	--
Mean	119	8024	8.43	7.08	25.62
SD		2683	2.82	2.37	4.17

These data show a relative bioavailability of 27% as compared to the data of FIG. 8.

Claims

We claim:

1. A drug delivery system for transbuccal delivery of a glucagon-like insulinotropic peptide to an individual's buccal mucosa comprising:

(a) a drug composition comprising an effective amount of a glucagon-like insulinotropic peptide and an effective amount of a permeation enhancer for enhancing permeation of said glucagon-like insulinotropic peptide through said buccal mucosa; and

(b) means for maintaining said drug composition in a drug transferring relationship with said buccal mucosa, wherein said drug composition and said maintaining means are combined in a single formulation.

2. The drug delivery system of Claim 1 wherein said system comprises a device of determined physical form.

3. The drug delivery system of Claim 2 wherein said device of determined physical form is a member selected from the group consisting of a patch and a tablet, and wherein said maintaining means is an adhesive.

4. The drug delivery system of claim 3 wherein said permeation enhancer is a member selected from the group consisting of cell envelope disordering compounds, solvents, steroidal detergents, bile salts, chelators, surfactants, non-surfactants, fatty acids, and mixtures thereof.

5. The drug delivery system of Claim 4 wherein said device of determined physical form is a tablet.

6. The drug delivery system of Claim 5 wherein said tablet comprises an adhesive layer comprising a

hydrophilic polymer having one surface adapted to contact a first tissue of the oral cavity and adhere thereto when wet and an opposing surface in contact with and adhering to an adjacent drug/enhancer layer comprising said permeation enhancer and said glucagon-like insulinotropic peptide, said drug/enhancer layer adapted to contact and be in drug transfer relationship with said buccal mucosa when said adhesive layer contacts and adheres to said first tissue.

7. The drug delivery system of claim 6 wherein said permeation enhancer is a bile salt comprising a steroidal detergent consisting of a member of the group consisting of natural and synthetic salts of cholanic acid and mixtures thereof.

8. The drug delivery system of claim 7 wherein said hydrophilic polymer comprises at least one member selected from the group consisting of hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethylcellulose, ethylcellulose, carboxymethyl cellulose, dextran, gaur-gum, polyvinyl pyrrolidone, pectins, starches, gelatin, casein, acrylic acid polymers, polymers of acrylic acid esters, acrylic acid copolymers, vinyl polymers, vinyl copolymers, polymers of vinyl alcohols, alkoxy polymers, polyethylene oxide polymers, polyethers, and mixtures thereof.

9. The drug delivery system of Claim 8 wherein said adhesive layer additionally contains one or more members selected from the group consisting of fillers, tableting excipients, lubricants, flavors, and dyes and wherein said drug/enhancer layer additionally contains one or members selected from the group consisting of tableting excipients, fillers, flavors, taste-masking agents, dyes, stabilizers, enzyme inhibitors, and lubricants.

10. The drug delivery system of Claim 9 wherein said bile salt enhancer is a salt of a conjugate of a bile acid with taurine.

11. The drug delivery system of Claim 10 wherein said hydrophilic polymer comprises a mixture of polyethylene oxide and polyacrylic acid.

12. The drug delivery stystem of Claim 11 wherein said first tissue is gingival tissue.

13. The drug delivery system of Claim 12 wherein said glucagon-like insulinotropic peptide is a member selected from the group consisting of GLP-1(7-36)amide and precursors, analogues, and fragments thereof.

14. The drug delivery system of claim 13 wherein said glucagon-like insulinotropic peptide is GLP-1(7-36)amide.

15. The drug delivery system of Claim 4 wherein said device of determined physical form is a matrix patch.

16. The drug delivery system of Claim 15 wherein said organic solvent is a member selected from the group consisting of a C_2 or C_3 alcohol, and C_3 or C_4 diol, DMSO, DMA, DMF, 1-n-dodecyl-cyclazacyclo-heptan-2-one, N-methyl pyrrolidone, N-(2-hydroxyethyl) pyrrolidone, triacetin, propylene carbonate and dimethyl isosorbide and mixtures thereof; said cell-envelope disordering compound is a member selected from the group consisting of isopropyl myristate, methyl laurate, oleic acid, oleyl alcohol, glycerol monoleate, glycerol dioleate, glycerol trioleate, glycerol monostearate, glycerol monolaurate, propylene glycol monolaurate, sodium dodecyl sulfate, and sorbitan esters and mixtures

thereof; and said bile salt is a steroidal detergent selected from the group consisting of natural and synthetic salts of cholanic acid and mixtures thereof.

17. The drug delivery system of Claim 16 wherein said glucagon-like insulinotropic peptide is a member selected from the group consisting of GLP-1(7-36)amide and precursors, analogues, and fragments thereof.

18. The drug delivery system of Claim 17 wherein said glucagon-like insulinotropic peptide is GLP-1(7-36)amide.

19. The drug delivery system of Claim 4 wherein said device of determined physical form is a liquid reservoir patch and wherein said drug composition is contained in said reservoir.

20. The drug delivery system of Claim 19 wherein said organic solvent is a member selected from the group consisting of a C_2 or C_3 alcohol, and C_3 or C_4 diol, DMSO, DMA, DMF, 1-n-dodecyl-cyclazacyclo-heptan-2-one, N-methyl pyrrolidone, N-(2-hydroxyethyl) pyrrolidone, triacetin, propylene carbonate and dimethyl isosorbide and mixtures thereof; said cell-envelope disordering compound is a member selected from the group consisting of isopropyl myristate, methyl laurate, oleic acid, oleyl alcohol, glycerol monoleate, glycerol dioleate, glycerol trioleate, glycerol monostearate, glycerol monolaurate, propylene glycol monolaurate, sodium dodecyl sulfate, and sorbitan esters and mixtures thereof; and said bile salt is a steroidal detergent selected from the group consisting of natural and synthetic salts of cholanic acid and mixtures thereof.

21. The drug delivery system of Claim 20 wherein said glucagon-like insulinotropic peptide is a member

and mixtures thereof; said cell-envelope disordering compound is a member selected from the group consisting of isopropyl myristate, methyl laurate, oleic acid, oleyl alcohol, glycerol monoleate, glycerol dioleate, glycerol trioleate, glycerol monostearate, glycerol monolaurate, propylene glycol monolaurate, sodium dodecyl sulfate, and sorbitan esters and mixtures thereof; and said bile salt comprises a steroidal detergent consisting of a member of the group consisting of natural and synthetic salts of cholanic acid and mixtures thereof.

29. The drug delivery system of Claim 28 wherein said glucagon-like insulinotropic peptide is a member selected from the group consisting of GLP-1(7-36)amide and precursors, analogues, and fragments thereof.

30. The drug delivery system of Claim 28 wherein said glucagon-like insulinotropic peptide is GLP-1(7-36)amide.

31. The drug delivery system of Claim 1 wherein said drug composition further comprises a sulfonyl urea.

32. A method of delivering a glucagon-like insulinotropic peptide for transbuccal drug delivery to an individual's buccal mucosa comprising bringing said buccal mucosa into contact with a delivery system comprising:

(a) a drug composition comprising an effective amount of said glucagon-like insulinotropic peptide and an effective amount of a permeation enhancer for enhancing permeation of said glucagon-like insulinotropic peptide through said buccal mucosa; and

(b) means for maintaining said drug composition in a drug transferring relationship with said buccal

mucosa, wherein said drug composition and said maintaining means are combined in a single formulation;

and retaining said delivery system in contact with said mucosa for a time sufficient to delivery an effective amount of said peptide to said individual.

33. The method of Claim 32 wherein said system comprises a device of determined physical form.

34. The method of Claim 33 wherein said device of determined physical form is a member selected from the group consisting of a patch and a tablet, and wherein said maintaining means is an adhesive.

35. The method of claim 34 wherein said permeation enhancer is a member selected from the group consisting of cell envelope disordering compounds, solvents, steroidal detergents, bile salts, chelators, surfactants, non-surfactants, fatty acids, and mixtures thereof.

36. The method of Claim 35 wherein said device of determined physical form is a tablet.

37. The method of Claim 36 wherein said tablet comprises an adhesive layer comprising a hydrophilic polymer having one surface adapted to contact a first tissue of the oral cavity and adhere thereto when wet and an opposing surface in contact with and adhering to an adjacent drug/enhancer layer comprising said permeation enhancer and said glucagon-like insulinotropic peptide, said drug/enhancer layer adapted to contact and be in drug transfer relationship with said buccal mucosa when said adhesive layer contacts and adheres to said first tissue.

38. The method of claim 37 wherein said permeation enhancer is a bile salt comprising a steroidal detergent consisting of a member of the group consisting of natural and synthetic salts of cholanic acid and mixtures thereof.

39. The method of claim 38 wherein said hydrophilic polymer comprises at least one member selected from the group consisting of hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethylcellulose, ethylcellulose, carboxymethyl cellulose, dextran, gaur-gum, polyvinyl pyrrolidone, pectins, starches, gelatin, casein, acrylic acid polymers, polymers of acrylic acid esters, acrylic acid copolymers, vinyl polymers, vinyl copolymers, polymers of vinyl alcohols, alkoxy polymers, polyethylene oxide polymers, polyethers, and mixtures thereof.

40. The method of Claim 39 wherein said adhesive layer additionally contains one or more members selected from the group consisting of fillers, tableting excipients, lubricants, flavors, and dyes and wherein said drug/enhancer layer additionally contains one or members selected from the group consisting of tableting excipients, fillers, flavors, taste-masking agents, dyes, stabilizers, enzyme inhibitors, and lubricants.

41. The method of Claim 40 wherein said bile salt enhancer is a salt of a conjugate of a bile acid with taurine.

42. The method of Claim 40 wherein said hydrophilic polymer comprises a mixture of polyethylene oxide and polyacrylic acid.

43. The method of Claim 42 wherein said first tissue is gingival tissue.

61. The method of Claim 60 wherein said glucagon-like insulinotropic peptide is GLP-1(7-36)amide.

62. The method of Claim 32 wherein wherein said drug composition further comprises a sulfonyl urea.

63. A method of treating diabetes comprising delivering a glucagon-like insulinotropic peptide for transbuccal delivery to an individual's buccal mucosa comprising bringing the buccal mucosa into contact with a delivery system comprising:

(a) a drug composition comprising an effective amount of the glucagon-like insulinotropic peptide and an effective amount of a permeation enhancer for enhancing permeation of the glucagon-like insulinotropic peptide through the buccal mucosa; and

(b) means for maintaining the drug composition in a drug transferring relationship with the buccal mucosa, wherein the drug composition and the maintaining means are combined in a single formulation;

and retaining said delivery system in contact with said mucosa for a time sufficient to delivery an effective amount of said peptide to said individual.

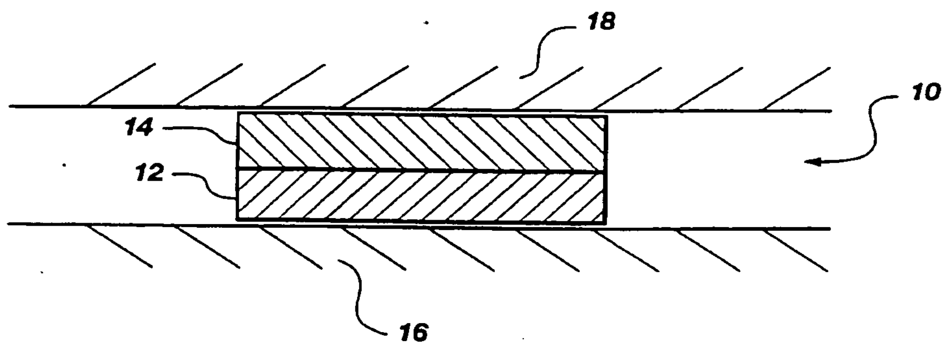
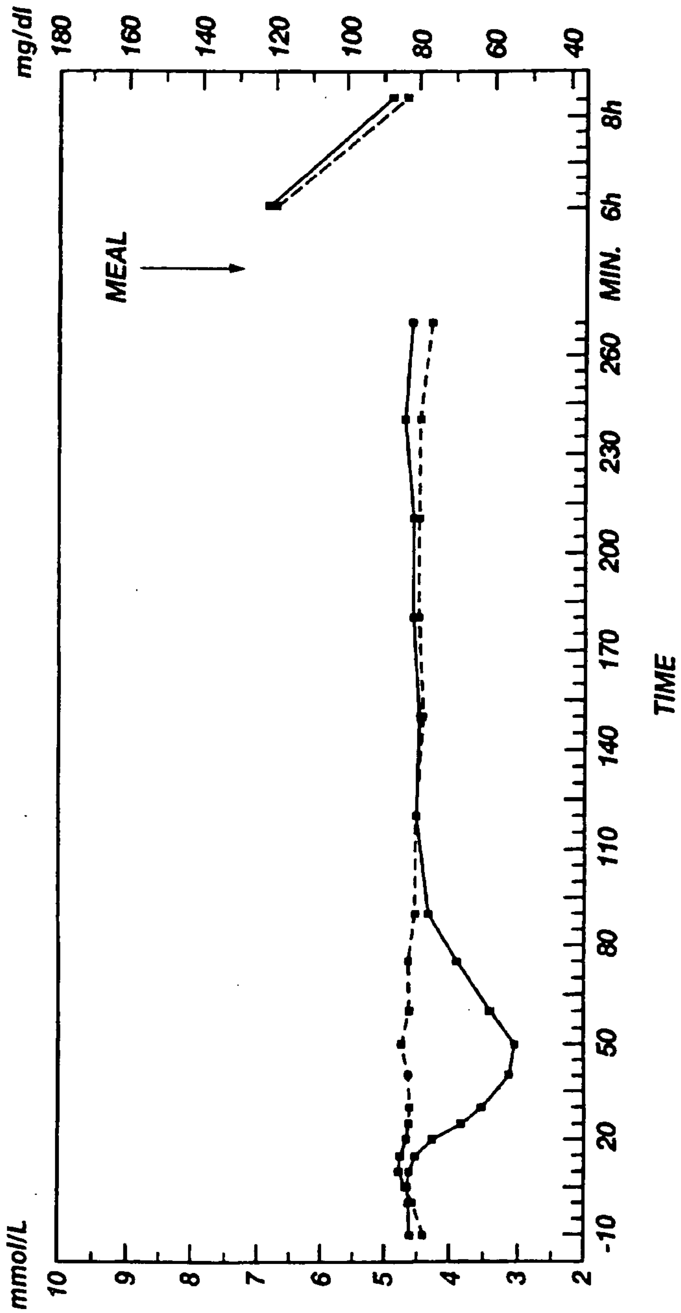


Fig. 1

3/7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140
120
100
80
60
40
mmol/L
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9
8
7
6
5
4
3
2
MEAL
-10
20
50
80
110
140
170
200
230
260
MIN.
6h
8h
TIME

Fig. 4

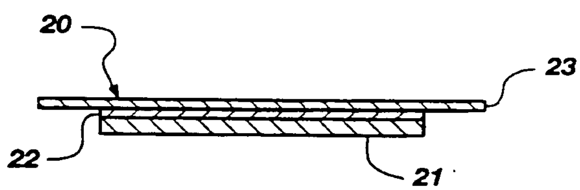


Fig. 2

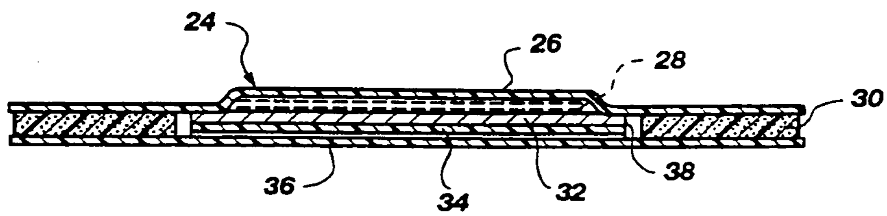
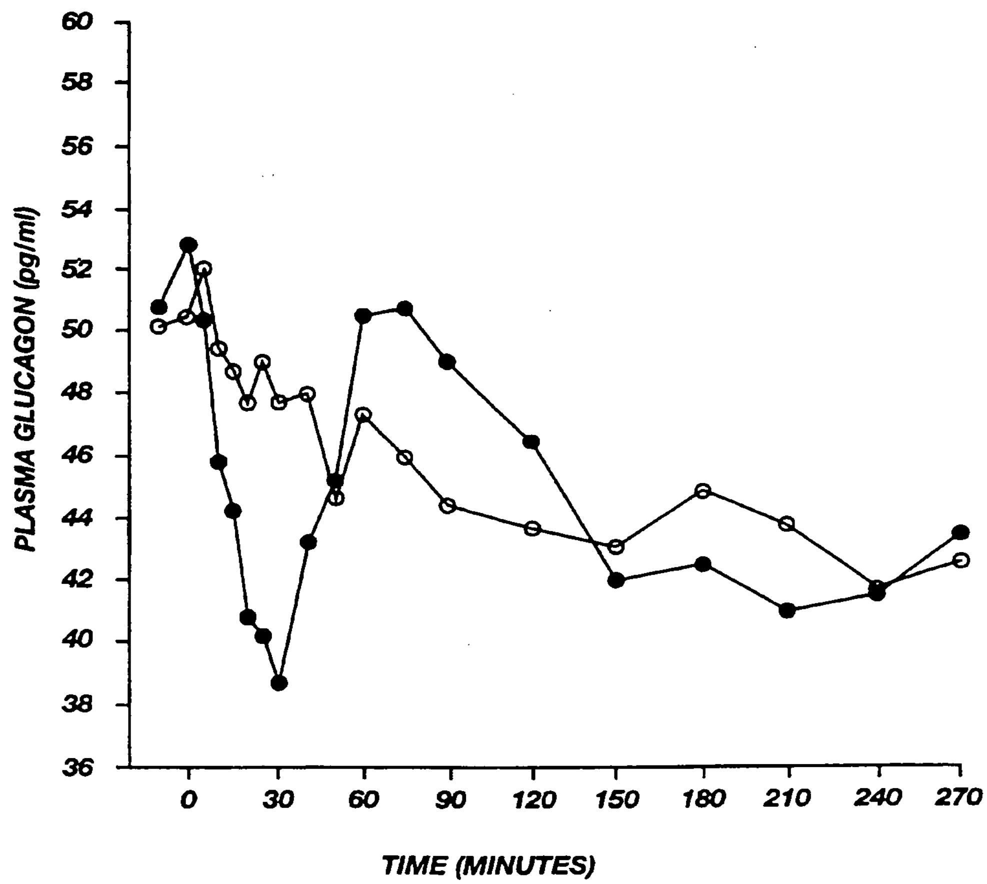


Fig. 3



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54
52
50
48
46
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38
36
0
30
60
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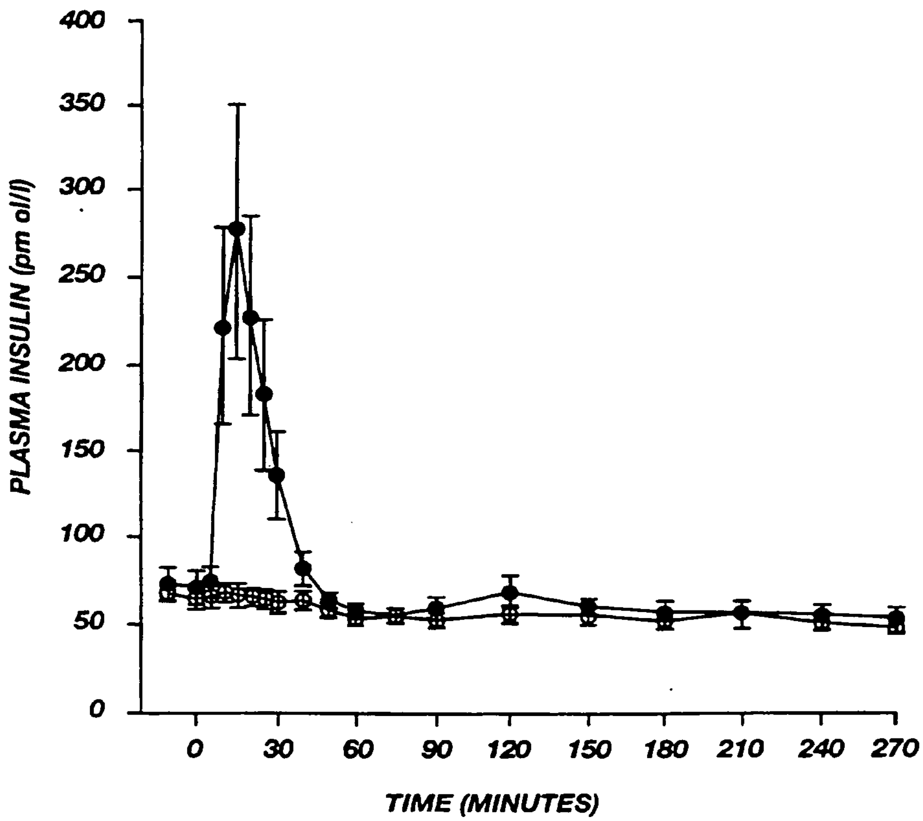
150
180
210
240
270
TIME (MINUTES)

Fig. 6



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210
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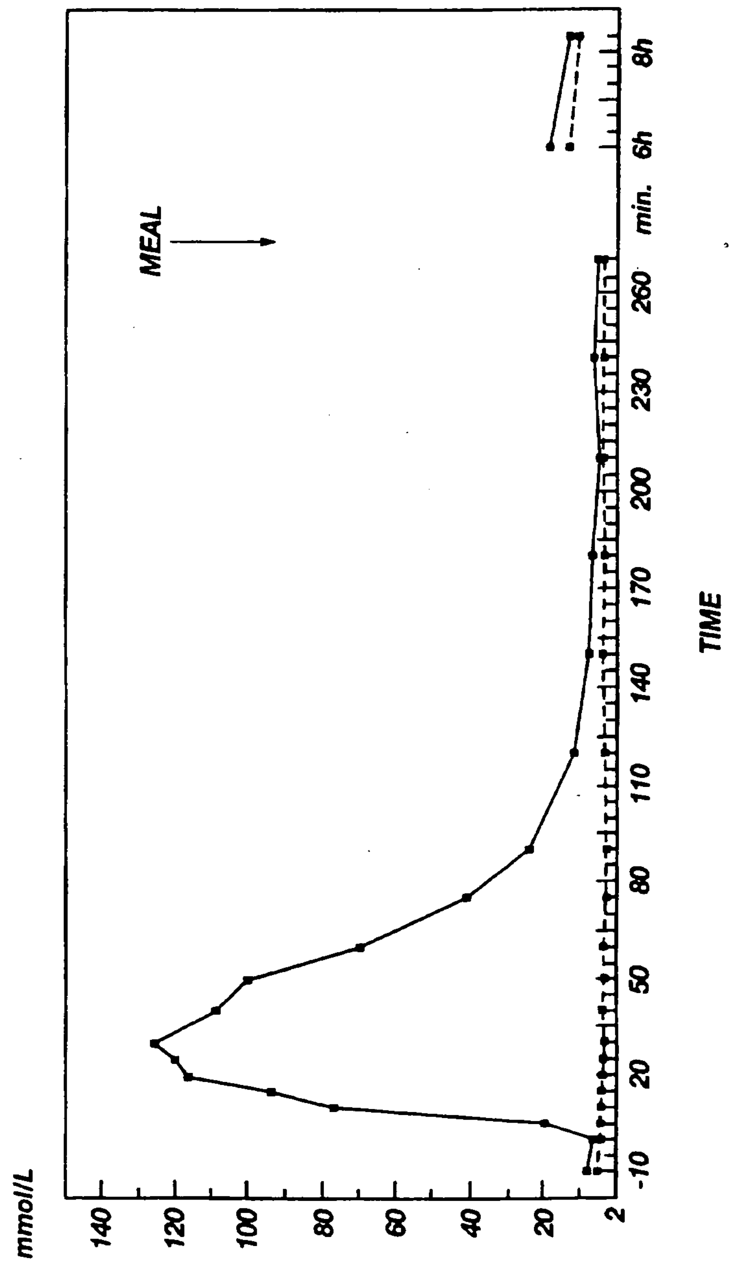
270
TIME (MINUTES)

Fig. 5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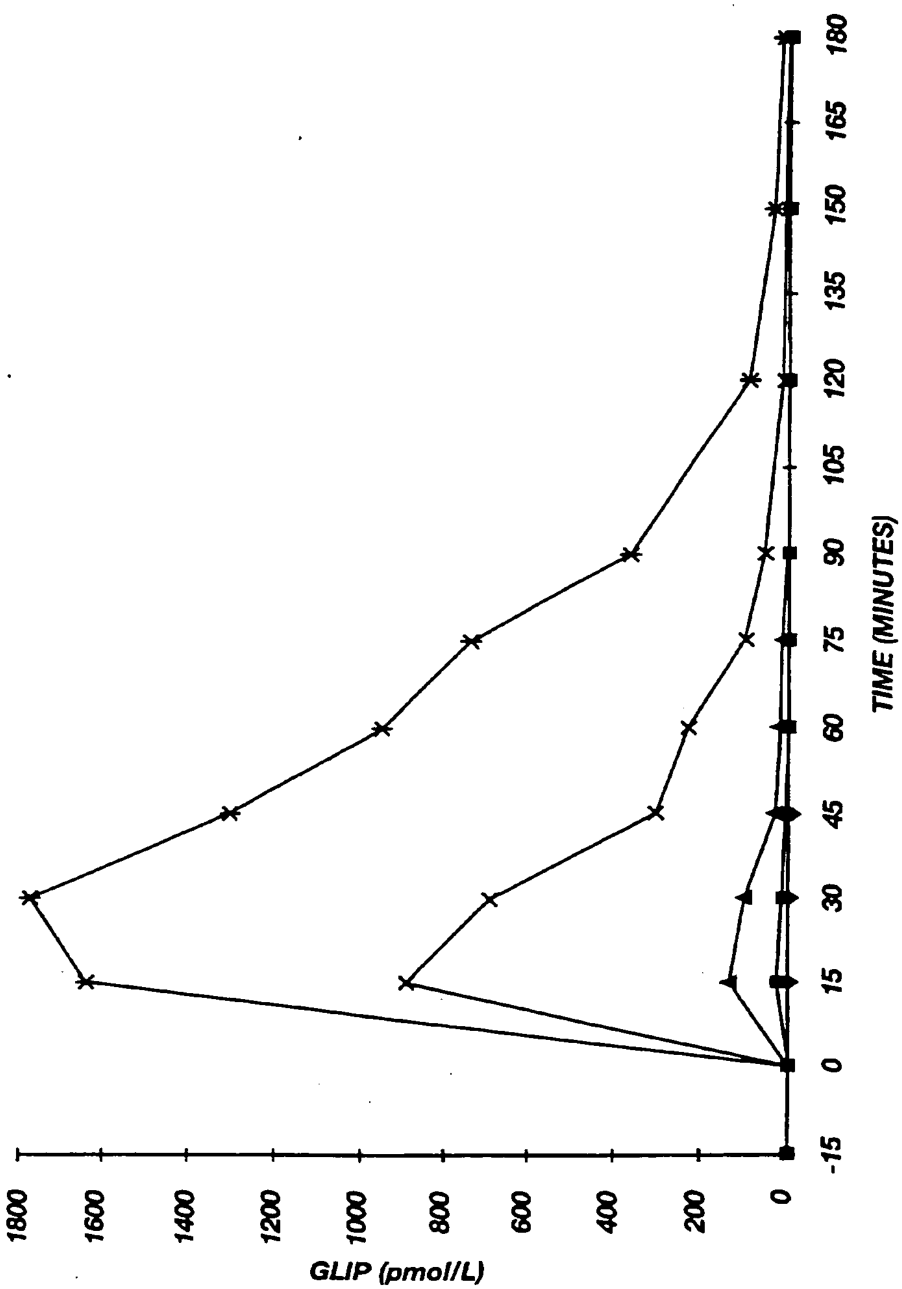
min.
6h
8h
MEAL
TIME

Fig. 7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1200
1000
800
600
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200
0
TIME (MINUTES)
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75
90
105
120
135
150
165
180

Fig. 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/16890

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 9/70; A61L 15/16
US CL : 424/434, 445, 449
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/434, 445, 449

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 619 322 A2 (PFIZER INC.) 10 December 1994, see entire document	1-63

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
04 DECEMBER 1996	17 JAN 1997

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	TW for Carlos Azpuru
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